Citation:

Laaksonen DE, Nyyssönen K, Niskanen L, Rissanen TH, Salonen JT. Prediction of cardiovascular mortality in middle-aged men by dietary and serum linoleic and polyunsaturated fatty acids. *Arch Intern Med*. 2005 Jan 24; 165(2): 193-199.

PubMed ID: 15668366

Study Design:

Prospective Cohort Study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To assess the association of dietary fat quantity and quality, specifically linoleic and α-linolenic acid, with cardiovascular disease (CVD) and overall mortality during a 15-year follow-up in a population-based cohort of middle-aged men who were free of CVD, cancer and diabetes at baseline.

Inclusion Criteria:

Not described.

Exclusion Criteria:

- Men with a history of CVD, diabetes or cancer at baseline
- Men with missing data for both dietary and serum fatty acids.

Description of Study Protocol:

Design

Prospective cohort study.

Dietary Intake/Dietary Assessment Methodology

Participants dietary intake was determined using four-day food records that were collected on three week days and one weekend day.

Statistical Analysis:

- Dietary variables from the four-day food records were recorded as "grams per day" or

"milligrams per day" and adjusted by total energy intake before further analysis
- Because plasma vitamin E is strongly associated with serum lipid and lipoprotein concentrations, α-tocopherol concentrations were standardized for LDL, HDL and triglycerides
- Associations of serum fatty acids proportions and dietary linoleic acid categorized into thirds were analyzed with forced Cox proportional hazard models. Variables with a skewed distribution (serum insulin, C-reactive protein, triacylglycerol, dietary fat and dietary fatty acids) were natural log transformed for analyses involving continuous variables
- Covariates with missing values were assigned the group mean
- Statistical significance was set at $P<0.05$.

Data Collection Summary:

Timing of Measurements

- Baseline information, including dietary intake data, was collected from 1984 to 1989
- Follow-up assessment of mortality was conducted through December 2001.

Dependent Variables

Deaths were ascertained using the national death registry using Finnish social security number. Deaths were coded according to the International Classification of Disease, Ninth Revision. Deaths coded as CHD or stroke were validated using the international criteria adopted by the World Health Organization (WHO).

Independent Variables

- Dietary fat intake was determined using four-day food records
- Serum fatty acids were determined using blood sampling at baseline.

Control Variables

Medical history, medications, family history of diseases, smoking, alcohol consumption, adult socioeconomic status, blood pressure, leisure-time physical activity and body mass index (BMI) were measured.

Description of Actual Data Sample:

- *Initial N:* N=2,682 men who were 42, 48, 54, or 60 years of age at baseline
- *Attrition (final N):* N=1,551
- *Age:* Men were 42, 48, 54, or 60 years of age at baseline. Mean age 52 years
- *Other relevant demographics:*
  - Socioeconomic status was rated as a 0.56 on a scale of zero to 1.0, low to high
  - 31% were smokers
  - 44% had a family history of CHD
  - 10% were taking blood pressure medication
- *Anthropometrics:* Mean BMI=26.5±3.4kg/m^2
- Location: Finland.

Summary of Results:

Subjects

- The median follow-up time was 14.6 years (range, 0.8 to 17.8 years), representing 22,645 person years
- During follow-up, 78 men died of CVD and 225 died of any cause
- Smoking, blood pressure, BMI and C-reactive protein were positively associated with CVD or overall mortality, and socioeconomic status, plasma vitamin E, plasma ascorbic acid and dietary fiber intake were inversely associated
- Men with lower dietary intake of linoleic and α-linolenic acid and PUFA had a higher CVD and overall mortality after adjustment for age and year of examination ($P<0.01$ to $P<0.05$)
- Proportions of esterified linoleic acid and α-linolenic acid and total PUFA and proportions of nonesterified linoleic acid were also inversely associated with death from CVD or any cause ($P<0.001$ to $P<0.05$)
- Intake of total fat, saturated fat, monounsaturated fat and cholesterol were not associated with CVD.

Fatty Acid Correlations

- Dietary linoleic acid intake was correlated with non-esterified ($R=0.34$) and esterified ($R=0.49$) linoleic acid proportions
- Total PUFA intake was composed of 77% dietary linoleic acid and was highly correlated with total PUFA intake ($R=0.95$)
- Dietary PUFA and saturated fat intake were inversely correlated ($R=-0.34$)
- Dietary PUFA and serum PUFA esterified proportions were also correlated ($R=0.50$).

Dietary Fatty Acids and CVD Mortality

- Men with dietary linoleic acid intake in the upper third were up to 61% less likely to diet of CVD than their counterparts whose intake was in the lower third after adjusting for age and year of examination (RR=0.39, 95% CI: 0.19 to 0.1, $P<0.01$)
- α-linolenic acid was not significantly associated with CVD mortality
- Dietary PUFA intake in the upper third was associated with up to 62% lower risk of CVD mortality after adjustment for age and year of examination (RR=0.38, 95% CI: 0.20 to 0.70, $P<0.001$).

Dietary Fatty Acids and Overall Mortality

- Dietary linoleic acid intake was associated with a lower overall mortality during follow-up after adjusting for age and examination year (RR=0.66, 95% CI: 0.48 to 0.92, $P<0.06$), but not significantly after adjusting for lifestyle or dietary factors
- Total PUFA and α-linolenic acid intake were not associated with overall mortality.

Serum Fatty Acids and CVD Mortality

The associations of serum esterified fatty acid proportions with CVD mortality mirrored those of dietary fatty acids recorded in the food diary.

Serum Fatty Acids and Overall Mortality

- Esterified linoleic acids proportions were associated with a lower overall mortality ($R=0.44$, 95% CI: 0.30 to 0.67, $P<0.001$ for upper third vs. lower third)
- The inverse associations for proportions of *n*-6 fatty acids and especially PUFA were even stronger and significant in all models ($P<0.001$ to $P<0.02$)

- Esterified α-linolenic acid proportions had a borderline association with overall mortality after adjustment for age and year of examination (upper vs. lower third, R=0.72, 95% CI: 0.51 to 1.03, P=0.95), but not after adjustment of potential confounding or mediating variables.

Author Conclusion:

The authors conclude that dietary polyunsaturated and, more specifically, linoleic fatty acid intake may have a substantial cardioprotective benefit that is also reflected in overall mortality. Overall, dietary fat quality seems more important than fat quantity in the reduction of cardiovascular mortality in men.

Reviewer Comments:

None.

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes

2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	No
2.2.	Were criteria applied equally to all study groups?	???
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	???
3.	**Were study groups comparable?**	???
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	N/A
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	???
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	???
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	???
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes

5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes

7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	No
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes